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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,990	HOWE, ALAN	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-14,36 and 38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-14, 36 and 38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Amendment filed on 05/18/2007 in response to the previous Non-Final Office Action (12/18/2006) is acknowledged and has been entered.

Claims 1-4, 6-14, 36 and 38-46 are currently pending.

Rejections Withdrawn:

The rejection of claims 1-2, 6-9 and 38-39 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement are withdrawn in view of Applicants arguments.

The rejection of claims 1-3, 7-8 and 10 under 35 U.S.C. 102(e) as being anticipated by Savage et al. (US 6,670,159, 12/31/1997) are withdrawn in view of Applicants amendments.

The rejections of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Zachariou et al. (Journal of Protein Chemistry 1995; 14: 419-430), claim 6 under 35 USC 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Zhou et al. (J. Am. Soc. Mass Spectrom 2000; 11: 273-282), claim 9 under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Ehteshami et al. (J. Molecular Recognition 1996; 9: 733-737, of record), and claims 36 and 38-39 under 35 U.S.C. 103(a) as being unpatentable over Savage et al. (US 6,670,159, 12/31/1997) in view of Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, of record) are withdrawn in view of Applicants arguments or amendments thereto.

New Rejections Necessitated by Amendment:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-9 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by McHahan *et al.* (Analytical Biochemistry 1996; 236: 101-106, *of record*).

McMahan et al. disclose a conjugate comprising polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical to identical to the molecule shown in the instant specification in Figure 7 (see page 103, Figure 1). For example, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, McMahan *et al.* teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan *et al.* teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Although McHahan *et al.* does not specifically teach that polydentate chelator, e.g. nitriloacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as NTA, nitrilloacetic acid, coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). For example, the specification teaches that in one embodiment, the presently claimed subject matter comprises a chelator-metal ion moiety that comprises Fe 3+ coordinated with NTA (page 19, lines 13-15). As such, the nitrilloactetic acid polydentate would inherently bind Fe3+, Al 3+, Yb 3+ and Ga 3+. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of

performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-3, 6-9, 36, 38-39 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*) as evidenced by McMahan *et al.* (*supra*).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Although Molecular Probes does not specifically teach that the detectable moiety is conjugated to the polydentate chelator at a site other than a potential metal ion coordination site, the claimed limitation does not appear to result in a manipulative difference between the claimed product and that disclosed by the prior art because the specification teaches that biotin-conjugated NTA is commercially available through Molecular probes or can be synthesized following the method of McMahan (described above). Thus, the conjugate appears to be free of the prior art. Similarly, while Molecular Probes does not specifically teach that the conjugate is soluble in an aqueous medium, the claimed functional limitation would be an inherent property of the referenced product because as evidenced by McMahan *et al.* (*supra*), biotin and nitriloacetic acid conjugates are soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Thus, the claimed "conjugate" appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10

USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Furthermore, although Molecular Probes does not specifically teach that polydentate chelator, e.g. nitriloacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as NTA, nitrilloacetic acid, coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). For example, the specification teaches that in one embodiement, the presently claimed subject matter comprises a chelator-metal ion moiety that comprises Fe 3+ coordinated with NTA (page 19, lines 13-15). As such, the nitrilloactetic acid polydentate would inherently bind Fe3+, Al 3+, Yb 3+ and Ga 3+. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-2, 4, 6-9 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Ehteshami *et al.* (J. Molecular Recognition 1996; 9: 733-737, *of record*).

Ehtashami *et al.* disclose a conjugate comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical which respect to the conjugation site as shown in the specification in Figure 7 D (page 734, Figure 1). With regards to the polydentate chelator, the reference teaches that the chelator is iminodiacetic acid (abstract). With regards to the detectable moiety, Ehtashami *et al.* teach (abstract) that the detectable moiety is

biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, Ehteshami *et al.* teach that the conjugate further comprises a PEG spacer between the chelator-metal ion moiety and the detectable label, wherein the presence of the PEG provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). Although Ehtashami *et al.* does not specifically teach that polydentate chelator, e.g. iminodiacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as IDA coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claims 1-2, 4, 6-14 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, *of record*).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a polydentate chelator moiety and a detectable moiety conjugated to the polydentate chelator moiety via a PEG spacer group. With regards to the polydentate chelator moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA). With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. Thus, while Etheshami does not specifically teach that the conjugate is soluble in an aqueous solution, the claimed functional limitation would be an inherent property of reference conjugate because as evidenced by Ehteshami *et al.* (supra), the presence of the PEG spacer between the chelator-metal ion moiety and the detectable label provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). Although Ehtashami *et al.* does not specifically teach that polydentate chelator, e.g. iminodiacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as IDA coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do

not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over McHahan et al. (Analytical Biochemistry 1996; 236: 101-106, *of record*), as applied to claims 1-3, 6-9 and 41 above, or Molecular Probes (MP 21879, Pro-Q™ Oligohistidine Blot Stain Kit #2, 09/27/2001, *of record*), 1-3, 6-9, 36, 38-39 and 41 above, in view of Neville et al. (Protein Science 1997; 6: 2436-2445, *of record*) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228, *of record*).

McMahan et al. disclose a conjugate comprising polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical to identical to the molecule shown in the instant specification in Figure 7 (see page 103, Figure 1). For example, the reference teaches (abstract, lines 5-7) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, McMahan *et al.* teach (abstract, lines 8-9) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, McMahan *et al.* teach that the conjugate further comprises a spacer between the chelator-metal ion moiety and the detectable label (page 103, Fig. 1). The reference further teaches that the conjugate is soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Lastly, the reference further teaches that the conjugate is a unique reagent, which can be used for the detection of histidine-tagged proteins (Title). Although McHahan *et al.* does not specifically teach

that polydentate chelator, e.g. nitriloacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as NTA, nitrilloacetic acid, coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). For example, the specification teaches that in one embodiment, the presently claimed subject matter comprises a chelator-metal ion moiety that comprises Fe 3+ coordinated with NTA (page 19, lines 13-15). As such, the nitrilloactetic acid polydentate would inherently bind Fe3+, Al 3+, Yb 3+ and Ga 3+. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Molecular Probes disclose a conjugate of the formula Biotin-X NTA comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the chelator-metal moiety, the reference teaches (page 1, 1st column, Introduction) that the chelator is nitriloacetic acid and the metal is Ni^{2+}. With regards to the detectable moiety, Molecular Probes teach (page 1, 1st column, Introduction) that the detectable moiety is biotin. The reference further teaches (Title) a kit comprising the conjugate comprising a chelator-metal ion moiety and a detectable moiety conjugated to the chelator-metal ion moiety. With regards to the kit, Molecular Probes teaches that the kit further comprises a secondary reagent for detecting the conjugate (1st page, 1st column, Introduction, lines 11-14), as well as instructions on how to use the kit. Although

Molecular Probes does not specifically teach that the detectable moiety is conjugated to the polydentate chelator at a site other than a potential metal ion coordination site, the claimed limitation does not appear to result in a manipulative difference between the claimed product and that disclosed by the prior art because the specification teaches that biotin-conjugated NTA is commercially available through Molecular probes or can be synthesized following the method of McMahan (described above). Thus, the conjugate appears to be free of the prior art. Similarly, while Molecular Probes does not specifically teach that the conjugate is soluble in an aqueous medium, the claimed functional limitation would be an inherent property of the referenced product because as evidenced by McMahan *et al.* (*supra*), biotin and nitriloacetic acid conjugates are soluble in an aqueous solution (page 104, beginning on 1st column, 1st paragraph to 2nd column). Thus, the claimed "conjugate" appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Furthermore, although Molecular Probes does not specifically teach that polydentate chelator, e.g. nitriloacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as NTA, nitrilloacetic acid, coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). For example, the specification teaches that in one embodiement, the presently claimed subject matter comprises a chelator-metal ion moiety that comprises Fe 3+ coordinated with NTA (page 19, lines 13-15). As such, the nitrilloactetic acid polydentate would inherently bind Fe3+, Al 3+, Yb 3+ and Ga 3+. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best

562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Neither McMahan et al. nor Molecular Probes teach that the metal ion is either Ga^{3+} or Fe^{3+}.

Nieba et al. teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to NTA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teaches that Fe^{3+} loaded NTA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag. For example, Neville et al. teaches that Fe^{3+} loaded NTA and IDA metal-ion affinity resin preferentially bound to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by McMahan et al. or Molecular Probes in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins which do not contain a His tag.

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ehteshami et al. (J. Molecular Recognition 1996; 9: 733-737), as applied to claims 1-2, 4, 6-9 and 41 above, in view of Neville et al. (Protein Science 1997; 6: 2436-2445) and Nieba et al. (Analytical Biochemistry 1997; 252: 217-228, *of record*).

Ehtashami *et al.* disclose a conjugate comprising a polydentate chelator and a detectable moiety conjugated to the polydentate chelator which appears to be identical which respect to the

conjugation site as shown in the specification in Figure 7 D (page 734, Figure 1). With regards to the polydentate chelator, the reference teaches that the chelator is iminodiacetic acid (abstract). With regards to the detectable moiety, Ehtashami *et al.* teach (abstract) that the detectable moiety is biotin. In addition to the conjugate comprising a chelator-metal ion moiety and a detectable label, Ehteshami *et al.* teach that the conjugate further comprises a PEG spacer between the chelator-metal ion moiety and the detectable label, wherein the presence of the PEG provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract). Although Ehtashami *et al.* does not specifically teach that polydentate chelator, e.g. iminodiacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as IDA coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Ehtashami et al. does not explicitly teach the metal ion as being either Ga^{3+} or Fe^{3+}.

Nieba et al. teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to IDA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teaches that Fe^{3+} loaded IDA metal-ion affinity resin preferentially bind to phosphopeptides as compared to His-containing peptides (abstract).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to substitute a metal ion such as Ga^{3+} or Fe^{3+} as taught by Neville et al. in view of Nieba et al. One would have been motivated to do so because as taught by Nieba et al., the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag. For example, Neville et al. teaches that Fe^{3+} loaded NTA and IDA metal-ion affinity resin preferentially bound to phosphoproteins as compared to His-containing peptides. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by substituting the metal ion as taught by Ehtashami et al. in view of Nieba et al., one would achieve a metal chelate which recognizes other proteins which do not contain a His tag.

Claims 40 and 42-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Etheshami (1996 "Synthesis and Characterization of Bioaffinity Interactive Heterobifunctional Polyethylene Glycols", Ph.D. dissertation, University of Arizona, of record), as applied to claims 1-2, 4, 6-14 and 41 above, in view of Nieba et al. (Analytical Biochemistry 1997; 252: 217-228, *of record*) and Neville et al. (Protein Science 1997; 6: 2436-2445, of record).

Etheshami et al. disclose (page 83 and 89) a conjugate comprising a polydentate chelator moiety and a detectable moiety conjugated to the polydentate chelator moiety via a PEG spacer group. With regards to the polydentate chelator moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA). With regards to the detectable moiety, Etheshami et al. teach (page 83) that the detectable moiety is biotin. The reference also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the

conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. Etheshami discloses (page 123, Chapter 5) a heterobifunctional poly (ethylene) glycol derivative having the structure biotin-PEG-IDA and its application in protein purification and characterization using a two phase system. Moreover, the dissertation teaches the effect of IDA in these biochelates for the separation of hemoglobin, a protein with a large number of surface accessible histidines that can interact with the immobilized metal ions and no affinity for biotin (page 126). With regards to the chelator-metal moiety, the reference teaches (page 89) that the chelator is iminodiacetic acid (IDA) and the metal is Cu2+. The dissertation also teaches (page 83-84) a method of synthesizing the conjugate comprising contacting iminodiacetic acid (IDA) with a molar excess of NHS-biotin under conditions wherein the biotin is transferred to IDA to form the chelator-detectable moiety complex. Etheshami further teaches (page 89) that the synthesis step further comprises mixing the IDA-PEG-Biotin conjugate in a metal ion containing solution, wherein the conjugate and metal ion are present in an equimolar concentration, i.e. 1:1. The reference further teaches that the conjugates are useful for immobilized metal affinity chromatography (IMAC) (abstract, page 20). Thus, while Etheshami does not specifically teach that the conjugate is soluble in an aqueous solution, the claimed functional limitation would be an inherent property of reference conjugate because as evidenced by Ehteshami *et al.* (supra), the presence of the PEG spacer between the chelator-metal ion moiety and the detectable label provides water solubility (abstract and page 733, *Introduction*, 1st column, lines 14-15). Although Ehtashami *et al.* does not specifically teach that polydentate chelator, e.g. iminodiacetic acid, coordinates a metal ion selected from the group consisting of Fe3+, Al 3+, Yb 3+ and Ga 3+, the claimed limitation does not appear to result in a manipulative difference between the claimed invention and the prior art because the specification teaches that the present invention encompasses polydentate chelators such as IDA coordinated to metal ions such as Fe3+, Al 3+, Yb 3+ and Ga 3+ (page 19, lines 1-11). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional

characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Moreover, because the claims do not appear to require the metal ion as being part of the phosphoprotein detection reagent, the teachings of the prior art meet the claimed limitations. Lastly, the intended use of the compound must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Ehtashami does not explicitly teach the metal ion is Fe^{3+}.

Nieba et al. teaches that while typically the metals Ni^{2+}, Zn^{2+}, Co^{2+}, and Cu^{2+} are chelated to IDA, the choice of the metal ion for IMAC are optimized for the highest selectivity relative to other proteins not carrying the His tag (page 217, 2nd column, 1st paragraph).

Neville et al. teach that Fe^{3+} loaded IDA metal-ion affinity resin binds acidic and poly-his peptides in addition to phosphopeptides (page 2437, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to optimize the metal taught by Etheshami et al. for Fe^{3+} in view of the teachings of Nieba and Neville et al. One would have been motivated to do so because each of the metal ions have been individually taught in the prior art to be successful at binding poly-his peptides. Thus, one of ordinary skill in the art would have a reasonable expectation that by substituting CU(II) as taught by Etheshami et al. for Fe3+ in view of the teachings of Nieba et al. and Neville et al., , one would achieve a metal chelate which recognizes poly-His peptides such as hemoglobin.

(Note: In order to expedite prosecution, the Examiner will address Applicants arguments pertaining the obviousness rejection of claims 1-2, 4 and 7-14 under 35 USC 103(a) as being unpatentable over the Ehteshami Dissertation in view of Neville et al. as it relates to the instant rejection.

In response to the previous rejection, Applicants assert that the Patent Office is basing the teachings of Ehteshami et al. by selective reading and is thus not viewing this reference in its entirety as required by MPEP 2141.03. In particular, Applicants assert that the reference to the pseudo-

affinity chelating effects disclosed on page 126 of the Ehteshami dissertation is intended to determine a background partitioning of a protein when the copper ion is added, and is not intended to identify a specific binding of the charged element. For example, Applicants assert that Chapter 5 of the Ehteshami Dissertation relates to experiments on bioligand-PEG-chelator reagents in a two phase system, wherein the bioligand is biotin or PAB, which are employed to bind to avidin or trypsin respectively. In particular, Applicants submit that the office appears to be relying on page 131 of the Ehteshami Dissertation, which experiments testing the ability of NH2-PEG-IDA and NH2-PEG-IDA-Cu(II) to partition avidin, for its assertion that the chelated metal ion binds to the ligand of interest, e.g., NH2-PEG-IDACU (II) has a higher partition coefficient that NH2-PEG-IDA. However, Applicants assert that this assertion is contrary to the disclose of Ehteshami Dissertation when the related discussion is considered in its entirety because it is clear from the passage, immediately following the cited passage, that the increased partition coefficient is an artifact and does not relate to the specific binding of avidin by the charged species as a result of the presence of the metal ion. In fact, Applicants assert that the Ehteshami Dissertation discloses on page 132 "as it can be seen from Table 5.1-2, the presence of the metal ions in bioligands-PEG-IDA-CUR has no significant effect on the partitioning of avidin". Therefore, Applicants assert that contrary to the Patent Office's assertions, the charged NH2-PEG-IDA-Cu(II) species does not bind to the ligand of interest via the chelated metal ion moiety.

These arguments have been carefully considered, but are not found persuasive.

First, the Examiner agrees with Applicants assertions with respect to Ehteshami teachings on page 131 and 132. However, as noted on page 26 of the Ehteshami Dissertation, these were not the only experiments, which were performed. For example, the Ehteshmi Dissertation on page 26 teaches that the "specificity of the bioligand moiety of these biopolymer (biotin and PAB) were tested by adding them to two-phase systems, without charging the chelate side with metal ion. Similarly, and in order to characterize the pseudo-affinity chelating effect, experiments were performed by charging it with metal ions first and then added to the two-phase systems, containing the protein, hemoglobin, rich in surface histidine (20 histidines) which has affinity for chelated metal ions, but having no affinity for PAB or biotin." Thus, as stated above, while the Examiner acknowledges that experiments were performed using avidin as the "target protein", the Examiner recognizes that the Ehteshami Dissertation is not limited only to these embodiments/examples.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Therefore, No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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